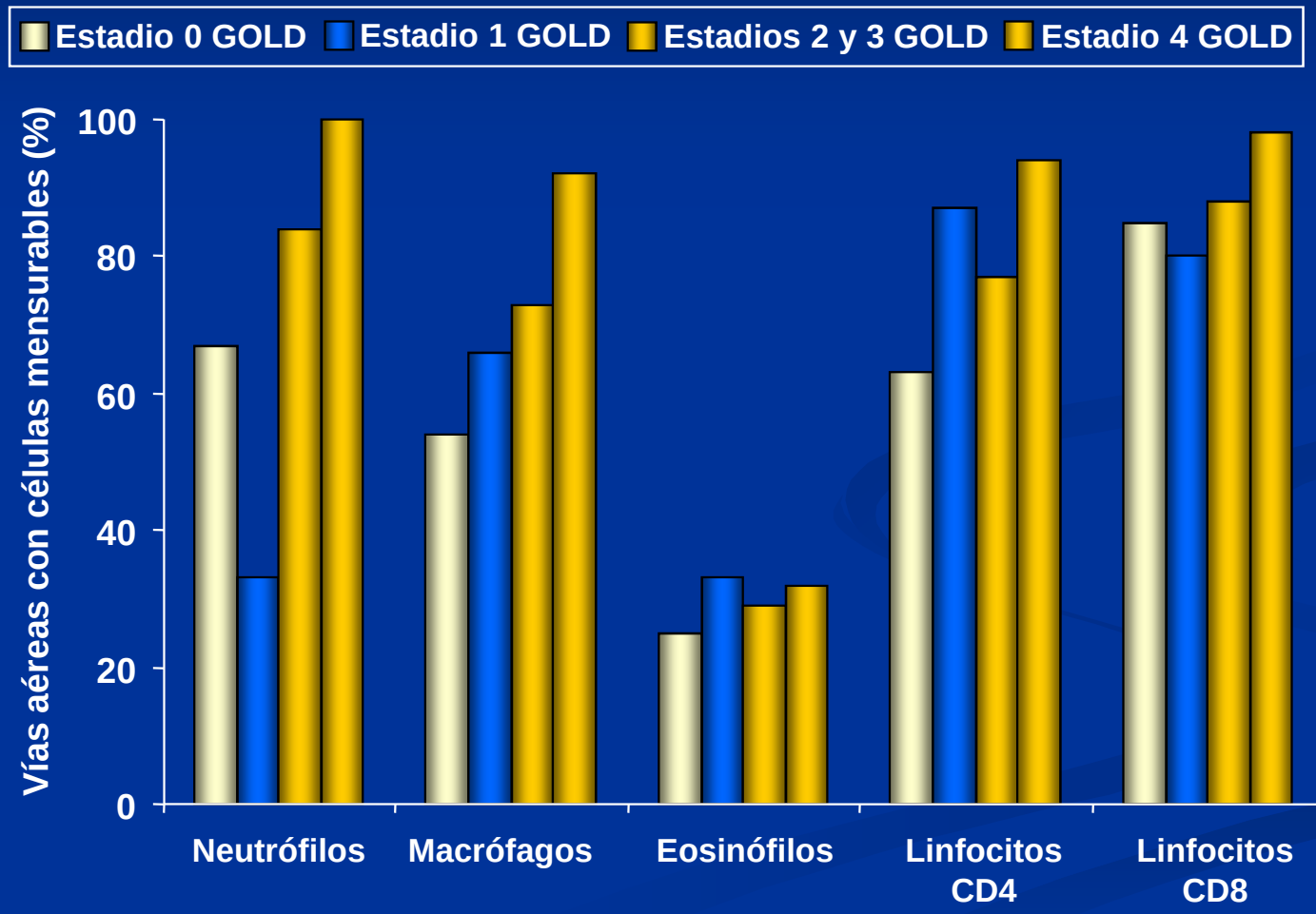
BIOMARCADORES EN EPOC

DR. GABRIEL ZUBILLAGA GARMENDIA
MEDICINA INTERNA
HOSPITAL UNIVERSITARIO DONOSTIA

BIOMARCADORES

- ¿Qué es un Biomarcador?: Marcador biológico medible (células, tejido, bioquímico, etc) objetivable como indicador de proceso normal, o proceso patogénico, o respuesta farmacológica a intervención.
- Esputo, Sangre, Biopsias, BAL, Orina, Aire exhalado, etc.

La cantidad de células y mediadores inflamatorios aumenta a medida que la enfermedad progresa



Hogg JC y cols. N Engl J Med 2004;350:2645-53.

EPOC → INFLAMACION LOCAL → INFLAMACION SISTEMICA

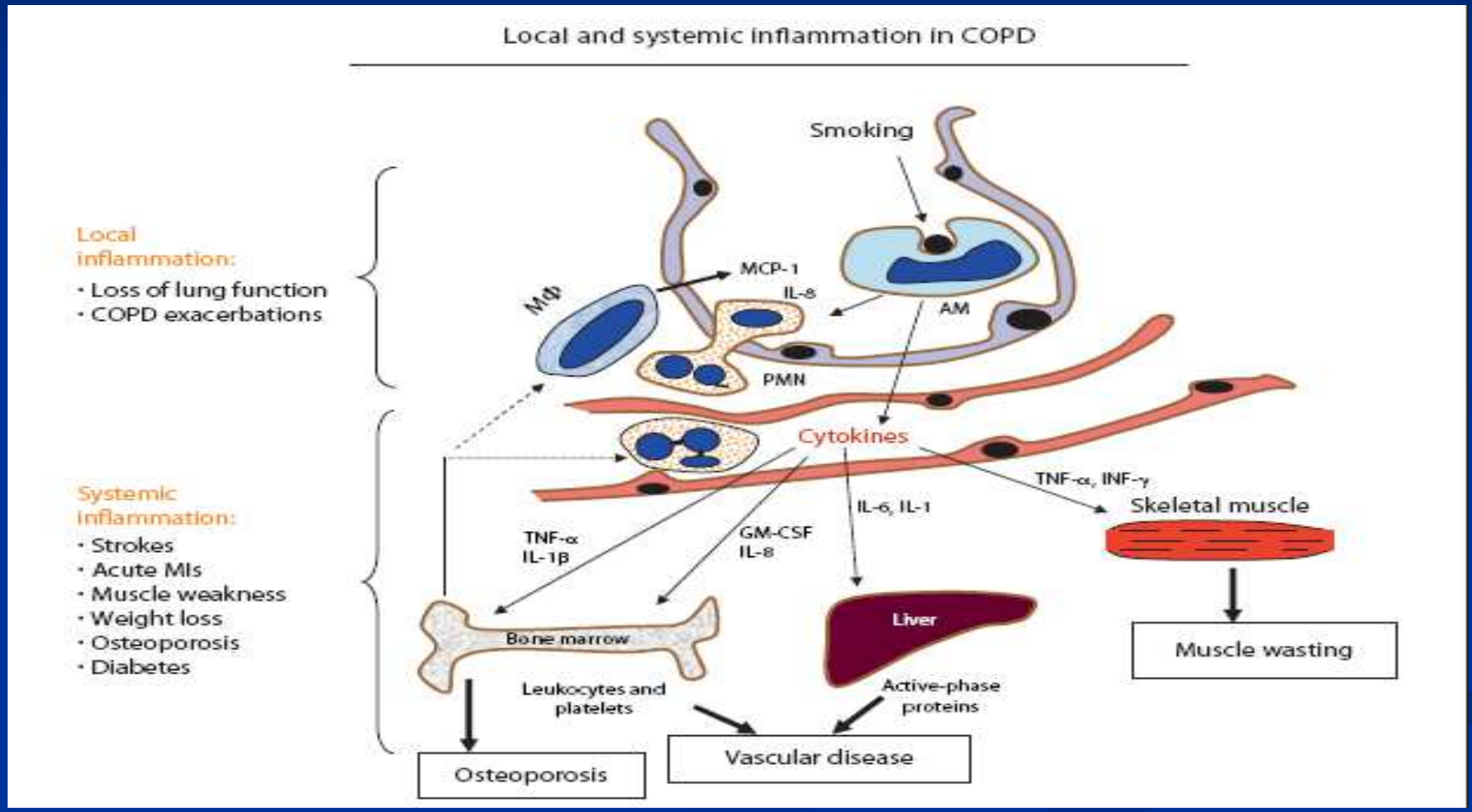


TABLE 2. DIFFERENCES IN PLASMA MARKERS BETWEEN BASELINE AND EXACERBATION

Marker	Units	Baseline Median (*IQR*)	Exacerbation Median (*IQR*)	Median (*% change*)	p Value (Wilcoxon)
CRP	mg/L	4.0 (2.0–12.0)	15.6 (4.5–74.0)	+185	**< 0.001**
IL-6	pg/ml	1.55 (0.94–3.07)	3.25 (1.48–6.12)	+66	**< 0.001**
MPIF-1	pg/ml	734 (574–944)	901 (72–1,237)	+18	**< 0.001**
PARC	pg/ml	1.1 (0.8–1.5) × 10^5	1.3 (0.9–1.7) × 10^5	+10	**0.002**
ACRP-30	pg/ml	1.5 (0.9–2.3) × 10^7	1.6 (1.1–2.6) × 10^7	+11	**0.001**
s-ICAM-1	pg/ml	4.8 (3.7–5.9) × 10^5	5.0 (4.1–6.4) × 10^5	+6	**0.003**
Amphiregulin	pg/ml	8.85 (5.86–11.40)	8.89 (5.87–12.30)	0	0.936
BDNF	pg/ml	4,958 (4,202–8,018)	4,921 (4,114–6,821)	−6	0.256
β-NGF	pg/ml	2.11 (0.78–4.46)	2.47 (0.94–4.16)	0	0.743
ENA-78	pg/ml	1,152 (752–1,934)	1,038 (814–1,751)	−4	0.358
Eotaxin-2	pg/ml	1,435 (944–2,052)	1,315 (978–1,911)	−7	0.029
Erb-B2	pg/ml	3,248 (2,827–4,002)	3,271 (2,703–4,121)	0	0.746
Fibronectin	pg/ml	3.0 (2.4–3.8) × 10^8	3.0 (2.2–4.0) × 10^8	+1	0.734
IFN-γ	pg/ml	1.2 (0.5–3.0)	1.6 (0.7–3.1)	−1	0.808
IL-1β	pg/ml	0.68 (0.40–0.95)	0.69 (0.45–1.10)	−1	0.343
IL-1Ra	pg/ml	61.1 (42.2–89.6)	71.2 (51.0–130.0)	+10	0.014
IL-2Rγ	pg/ml	26.9 (22.3–33.5)	29.6 (22.5–36.7)	+6	0.059
IL-8	pg/ml	2.5 (1.7–4.9)	2.6 (1.9–4.9)	−2	0.642
IL-12 p40	pg/ml	7.0 (4.9–10.7)	7.7 (4.4–14.9)	+2	0.385
IL-15	pg/ml	0.85 (0.60–1.10)	0.95 (0.63–1.30)	+9	0.065
IL-17	pg/ml	5.5 (2.9–9.6)	6.4 (3.5–9.8)	+8	0.351
IP-10	pg/ml	152 (106–234)	192 (137–252)	+20	0.011
ITAC	pg/ml	13.3 (0.8–13.9)	19.6 (1.6–39.2)	+1	0.232
MCP-1	pg/ml	444 (370–534)	439 (359–537)	−3	0.842
MIP-1β	pg/ml	57.8 (41.3–80.0)	59.6 (40.0–85.7)	−1	0.933
MMP-9	pg/ml	39,597 (25,802–85,597)	33,542 (23,284–56,772)	−6	0.689
MPO	pg/ml	11,417 (7,921–21,237)	13,280 (8,483–22,613)	−4	0.575
Prolactin	pg/ml	1,028 (710–1,499)	928 (689–1,298)	−3	0.103
RANTES	pg/ml	32,968 (20,641–58,916)	36,687 (22,341–52,693)	+10	0.161
L-selectin	pg/ml	7.6 (6.5–8.6) × 10^5	7.6 (6.5–8.5) × 10^5	−1	0.485
TGF-α	pg/ml	2.5 (1.3–4.5)	3.0 (1.5–4.8)	+7	0.308
TIMP-1	pg/ml	63,979 (50,733–76,540)	64,685 (51,946–75,712)	+1	0.734
TNF-α	pg/ml	1.9 (0.7–3.5)	1.8 (0.9–3.7)	+6	0.249
TNFR1	pg/ml	601 (445–773)	654 (507–926)	+11	0.011
TNFR2	pg/ml	1,580 (1,267–2,228)	1,627 (1,249–2,394)	+3	0.177
VEGF	pg/ml	0.01 (0.01–0.62)	0.01 (0.01–0.38)	0	0.725

Am J Respir Crit Care Med Vol 174. pp 867–874, 2006

COSTE DE BIOMARCADORES

- ***FUENTE INFORMACION/SERVICIO LABORATORIO DEL HOSPITAL/ REFERENCE***

- **<u>COSTE POR UNIDAD DE PRUEBA</u>:**
- **PCR alta sensibilidad: 15 €**
- **Fibrinógeno: 1,50 €**
- **TNF-α: 50 €**
- **IL-6: 36 €**
- **IL-8: 50 €**

CONCLUSION

- EPOC → INFLAM. LOCAL →INFLAM. SISTEMICA.
- CELULAS. CITOQUINAS. INTERLEUQUINAS. RECEPTORES. PROTEASAS. MEDIADORES INFLAMATORIOS. FACTORES DE TRANSCRIPCION. GENETICA.
- PCR. FIBRINOGENO. TNF-α. IL-6. IL-8. GASES EXHALADOS.
- REPERCUSION SISTEMICA: ↓PESO, MASA MUSCULAR, ANEMIA, OSTEOPOROSIS, DEPRESION, RIESGO VASCULAR, MALA CALIDAD DE VIDA, ↑MORTALIDAD, CANCER.

Biomarkers Associated With Increased COPD Susceptibility

Sputum
↑ neutrophils
↑ $CD8^+$ lymphocytes
↑ eosinophils
↑ MPO, HNL, NE, ECP, IL-8, LTB4, GRO-α MCP1, GM-CSF, TNF-α
↑ nitrogen oxides
↑ proteases, ↓ antiproteases

Exhaled breath condensate
↑ CO
↑ NO
↑ pentane
↑ ethane
↑ H_2O_2
↑ 8-isoprostane
↑ nitrogen, ↑ nitrosothiols
↑ LTB4, PGE-2

Blood
↑ neutrophilic respiratory burst
↑ monocytic CXCR2
↑ monocytic TGF-b
↑ Trolox equivalent antioxidant capacity
↑ fibrinogen

Urine
↑ 8-hydroxydeoxyguanosine
↑ desmosine

Bronchial biopsies-lavage fluid
↑ neutrophils
↑ $CD8^+$ lymphocytes
↑ eosinophils
↑ IL-8, MPO, ECP
↑ bronchial epithelial cell of GRO-α, IL-6, IL-8 IL-1b, sICAM-1
↑ alveolar macrophage release of IL-8, elastolytic enzymes

Tzortzaki EG, et al. *Clin Chim Acta*. 2006;364:124-138.

PCR como predictor Pronóstico

A) Estudio Copenhagen City Heart Study: 1302 sujetos población general seguidos 8 años.

- PCR inicial y constatar ingresos y muertes por EPOC.
  - Resultados: 14% hospitalizados, y 6% muerte.
  - PCR > 3 mg/l riesgo de morir 2,2 veces basal.
  - PCR < 3 mg/l riesgo de morir 1,4 veces basal.
- Mayores de 70 años, fumadores, FEV1 severo -Riesgo absoluto a 10 años de Ingreso Hospitalario: 54%, Muerte: 57%.

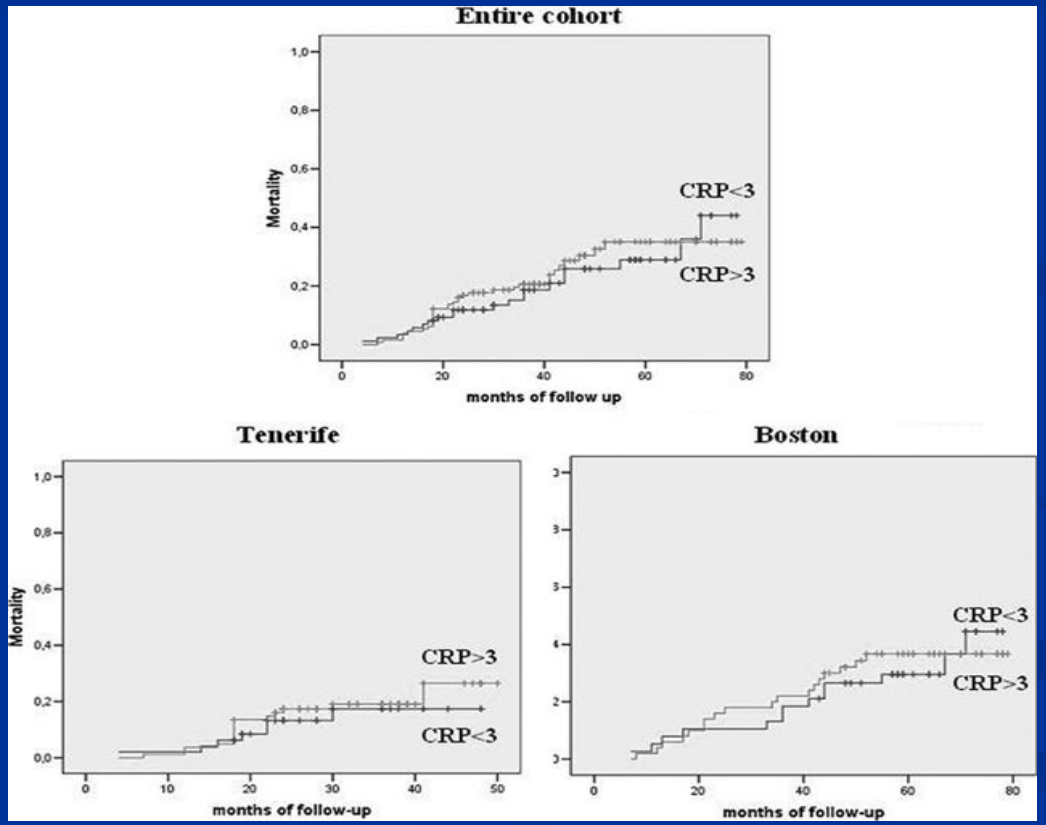
B) Estudio LHS: 4803 EPOC leve-moderada. Seguimiento 5 años.

- Resultados: Quintiles más elevados PCR: Riesgo 1,79 veces muerte.
- Eventos cardiovasculares y cáncer: 1,51 veces.
- Mayor descenso del FEV1 .
- PCR quintil mas alto vs bajo. RR: 4 (1 año), RR: 3,3 (2 años), RR: 1,8 (5 años).

Dahl AJRCCM 2007; 175: 250
Man THORAX 2006; 61: 849

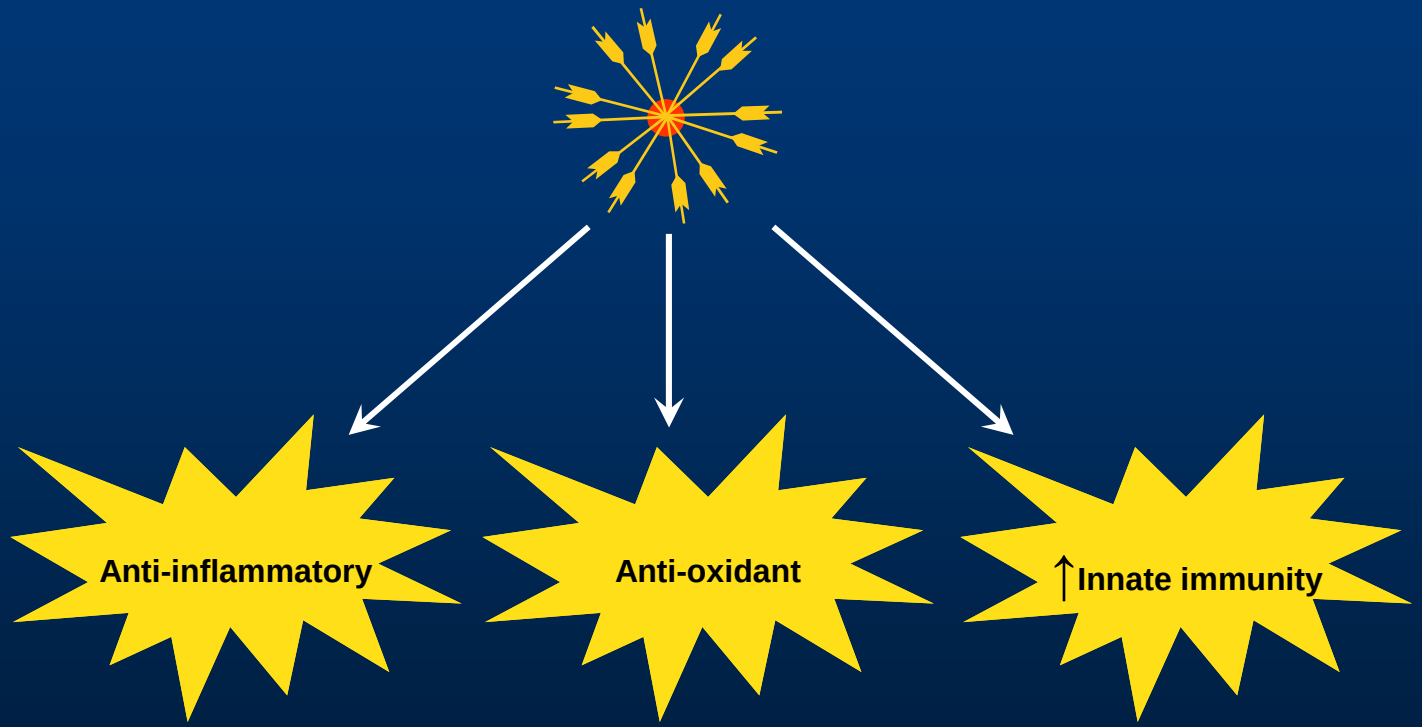
LA PCR MAS ELEVADA EN EPOC MODERADO-MUY SEVERO NO PREDICE MORTALIDAD

218 pacientes . SI ERA PREDICTOR EL INDICE BODE Y LA PaO2



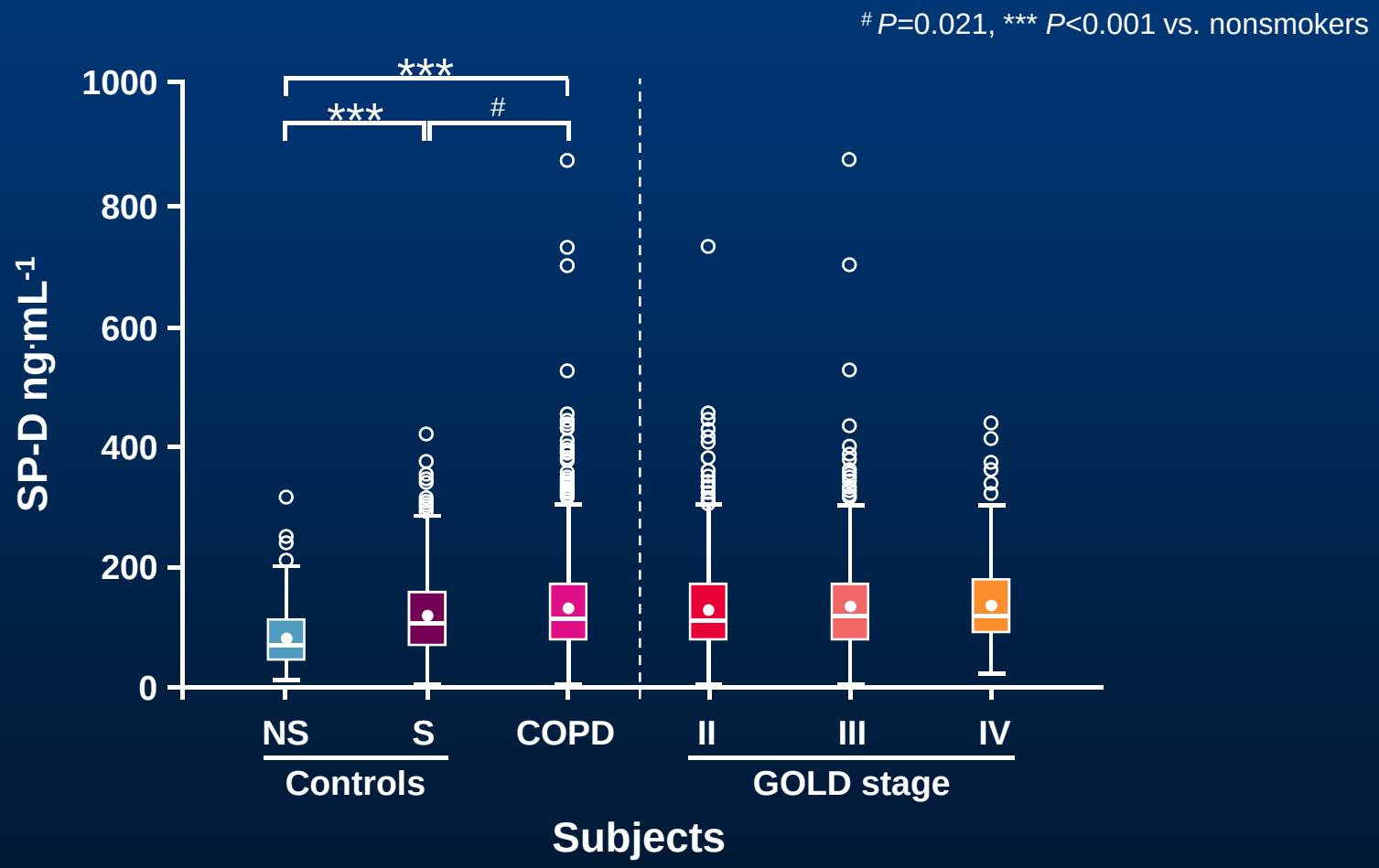
Juan de Torres Chest 2008; 133:1336

Actions of Surfactant Protein D



Sin DD, et al. *Ther Adv Respir Dis*. 2008;2:65-74. Reproduced with permission from SAGE Publications Ltd.

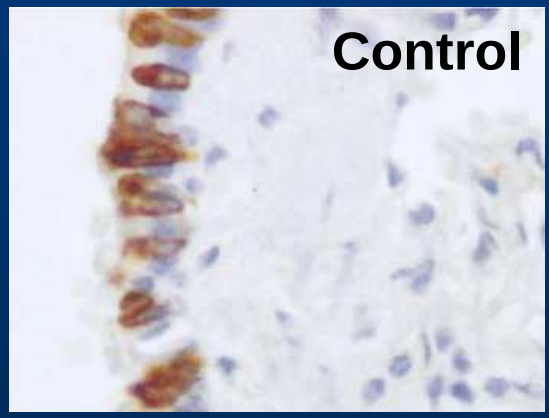
Surfactant Protein D Is Elevated in COPD Patients Versus Smokers and Nonsmokers

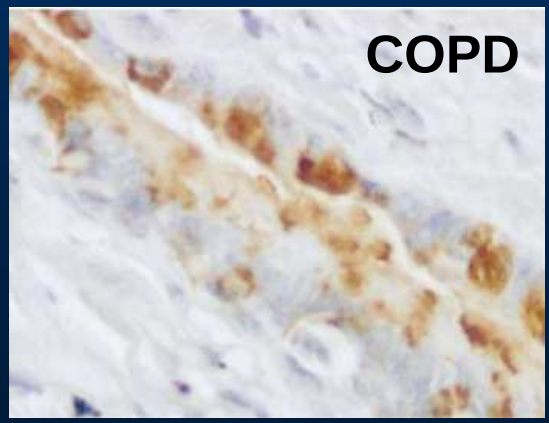


Lomas DA, et al. *Eur Respir J.* 2009;34:95-102.

Clara Cell Protein (CC16)

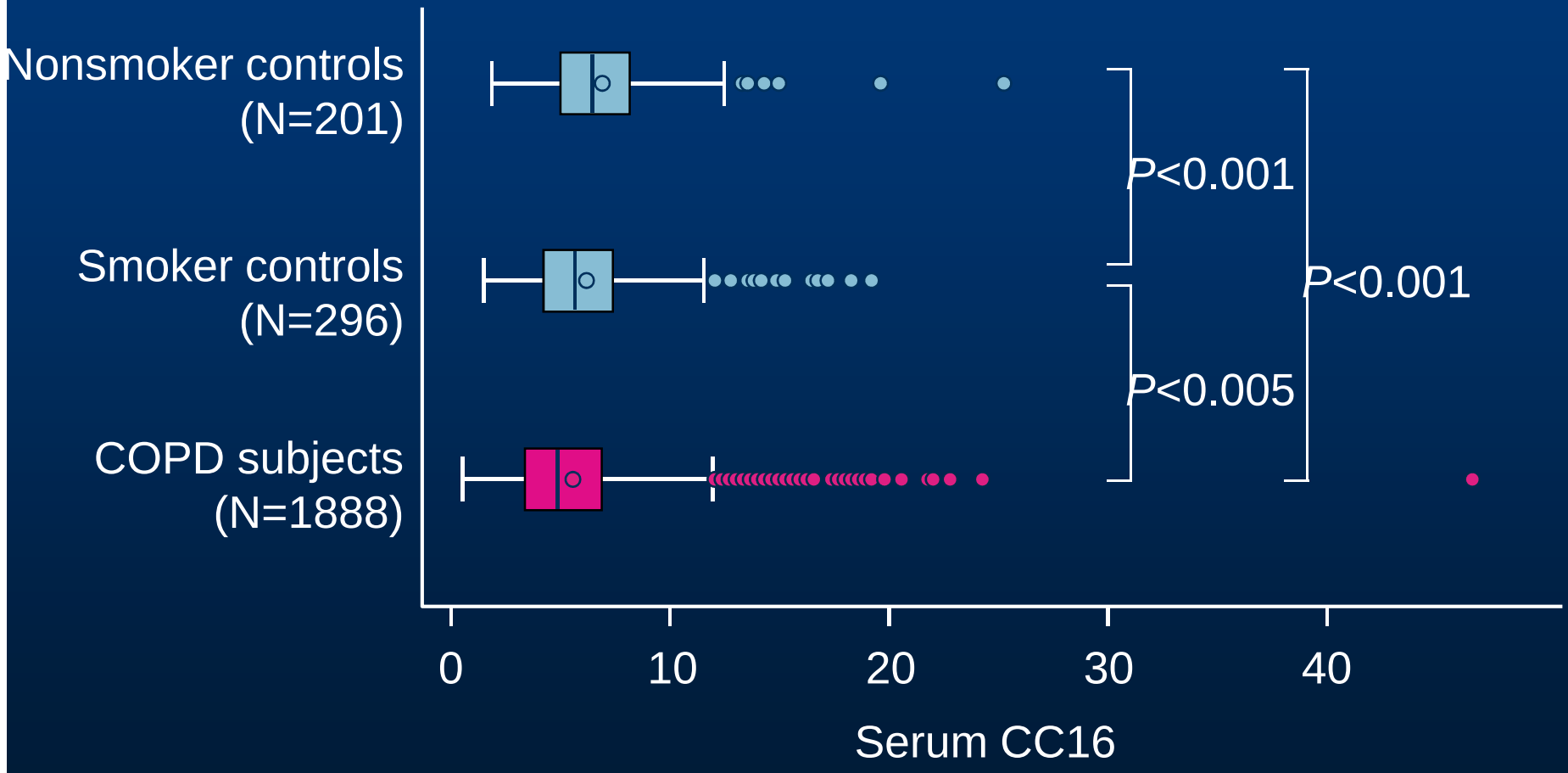
- Anti-inflammatory protein secreted by the non-ciliated bronchiolar Clara cells
- May have significant anti-inflammatory effects mediated by inhibition of phospholipase A2 and detoxification of xenobiotics
- Reduced expression in COPD





Pilette C, Godding V, Kiss R, et al. 2001. Reduced epithelial expression of secretory component in small airways correlates with airflow obstruction in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*. 163:185-194. Official Journal of the American Thoracic Society ©American Thoracic Society

CC16 Levels Are Decreased in COPD



Lomas DA, et al. *Thorax.* 2008;63:1058-1063. Permission requested.

Biomarkers Elevated During Exacerbations

Cytokine/marker	Patients with	
	Exacerbated COPD (*N*=30)	Stable COPD (*N*=30)
VEGFser (pg/mL)	602 (457-883)**	229 (151-310)
VEGFprp (pg/mL)	275 (169-431)**	118 (42-188)
VEGFppp (pg/mL)	22 (13-28)*	16 (13-19)
IL-6 (pg/mL)	3.5 (0.8-6.2)*	2.2 (1.7-2.9)
TNF-α (pg/mL)	1.0 (0.7-1.3)	1.3 (0.9-2.3)
CRP (mg/L)	6.0 (1-31)**	4.0 (2-6)
Fibrinogen (mg/dL)	419 (329-470)	424 (358-459)
PBNC count (x10^3 cells/μL)	9.5 (6-12)*	7.0 (5-9)
Haemoglobin (g/dL)	14.0 (13-15)	15.0 (13-16)
Platelet count (x10^3 cells/μL)	279 (194-356)	273 (218-316)

* $P<0.05$, ** $P<0.01$

Valipour A, et al. *Clin Sci*. 2008;115:225-232.

Biomarkers That Distinguish COPD Patients From Smokers

Marker	Nonsmoker vs COPD	Smoker vs COPD	Nonsmoker vs Smoker	Reference
Sputum macrophages (%)	Yes	Yes	No	Rufino R, et al. *J Bras Pneumol.* 2007;33:510-518.
Sputum neutrophils (%)	Yes	Yes	No	
Telomere length in leukocytes	Yes	Yes	No	Savale L, et al. *Am J Respir Crit Care Med.* 2009;179:566-571.
Sputum VEGF	Yes	Yes	ND	Rovina N, et al. *Respir Res.* 2007;8:53.
Sputum IL-8	Yes	Yes	ND	
Sputum TNF-α	Yes	No	ND	
Sputum MUC5AC	ND	Yes	ND	Kirkham S, et al. *Am J Respir Crit Care Med.* 2008;178:1033-1039.
MIP-1β in BALF	Yes	Yes	No	Capelli A, et al. *Eur Respir J.* 1999;14:160-165.
Sputum IL-18	Yes	Yes	Yes	Imaoka H, et al. *Eur Respir J.* 2008;31:287-297.
IL-32 in alveolar macrophages	Yes	Yes	Yes	Calabrese F, et al. *Am J Respir Care Med.* 2008;174;894-901.

ND = not done

Biomarkers That Distinguish COPD Patients From Smokers

Marker	Nonsmoker vs COPD	Smoker vs COPD	Nonsmoker vs Smoker	Reference
BALF YKL-40	Yes	Yes	Yes	Létuvé S, et al. *J Immunol*. 2008;181:5167-5173.[1]
Serum YKL-40	Yes	Yes	No	
Serum surfactant protein D	Yes	Yes	Yes	Lomas DA, et al. *Eur Respir J.* 2009;34:95-102.
Serum CC-16	Yes	Yes	Yes	Lomas DA, et al. *Thorax.* 2008;63:1058-1063.
Serum CRP	Yes	Yes	No	Pinto-Plata VM, et al. *Thorax.* 2006;61:23-28.
Serum TIMP	Yes vs. subjects without COPD, but matched smoking history		ND	Higashimoto Y, et al. *Eur Respir J.* 2005;25:885-890.
Plasma BNP	Yes	Yes	No	Inoue Y, et al. *Intern Med*. 2009;48:503-512.[6]
8-isoprostane in breath condensate	ND	Yes	ND	Montuschi P, et al. *Am J Respir Crit Care Med.* 2000;162:1175-1177.

ND = not done

ATS/ERS Conclusions Regarding Biomarkers

- Many pulmonary biomarkers have been described in COPD patients
- There is little information regarding reproducibility and correlation with other outcome measurements in COPD
  - Dyspnoea
  - Quality of life
  - Exacerbation frequency
  - Mortality
- Biomarkers must be assessed in COPD patients, normal smokers, and age-matched normal subjects and linked to:
  - Disease stage
  - Rate of FEV_1 decline
  - Clinical phenotype (emphysema vs. small airway disease)
  - Smoking status (current vs. ex-smokers)
  - Clinical status (stable vs. exacerbation)
  - Treatment (effect of corticosteroids, theophylline, etc.)

Cazzola M, et al. *Eur Respir J.* 2008;31:416-469.

COPD forum™

Future Evaluation of Biomarkers: ECLIPSE

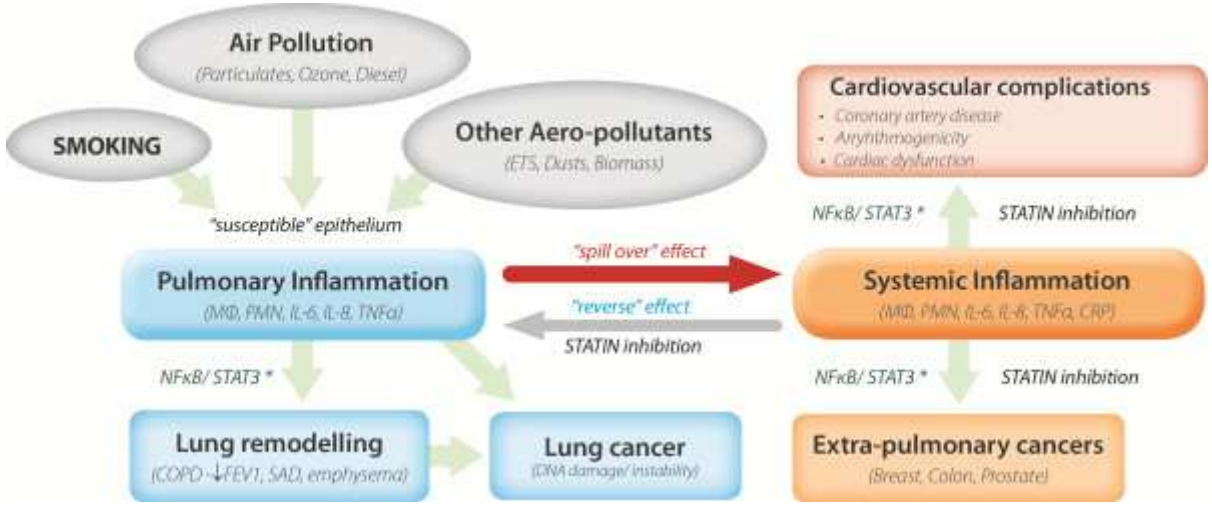
- Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) is a 3-year longitudinal study with four aims:
  - Definition of clinically relevant COPD subtypes
  - Identification of parameters that predict disease progression
  - Examination of biomarkers that correlate with COPD subtypes and may predict disease progression
  - Identification of novel genetic factors and/or biomarkers that both correlate with clinically relevant COPD subtypes and predict disease progression
- Subjects: 2,180 with GOLD Stage II–IV COPD, 343 smoking and 223 nonsmoking controls
- Assessments:
  - Pulmonary function measurements, chest CT, biomarker measurement (in blood, sputum, urine and exhaled breath condensate), health outcomes, body impedance, resting oxygen saturation, and 6-minute walking distance

Vestbo J, et al. *Eur Respir J*. 2008;31:869-873.

ESTUDIO ECLIPSE

Laboratory values	Odds Ratio	p
Platelet count — per increase of $10\times10_3/mm_3$	1.02 (1.01–1.04)	<0.001
White-cell count — per increase of $1\times10_3/mm_3$	1.07 (1.03–1.12)	<0.001
Neutrophil count — per increase of $1\times10_3/mm_3$	1.02 (1.01–1.03)	<0.001
Biomarkers		
Fibrinogen — mg/dl	1.35 (1.22–1.49)	<0.001
High-sensitivity C-reactive protein — mg/liter	1.24 (1.13–1.37)	<0.001
Chemokine ligand 18 — ng/ml	1.13 (1.02–1.25)	0.02
Surfactant protein D — ng/ml	1.10 (1.01–1.20)	0.04

Hurst et al. NEJM 2010; 363:12



Also of considerable importance, is the recent finding that elevated IL-6 or CRP levels are associated with increased risk of lung cancer [11], particularly in patients with COPD [12], and that lung cancer mortality is reduced by 17% with statin use . This is particularly the case as current inhaler therapy in COPD is symptom-based, minimizing breathlessness and reducing exacerbations, while statin-based systemic therapy, inhibiting both systemic and pulmonary inflammation, appears to confer significant disease modifying benefits. It also argues in favor of investigating the utility of measuring serum IL-6 (or it's surrogate CRP) in patients with COPD to target and monitor therapy. We conclude that the study of Ferrari and colleagues confirms earlier studies showing that outcomes in COPD are related to IL-6-mediated systemic inflammation [1].

Inflammatory Biomarkers and Comorbidities in Chronic Obstructive Pulmonary Disease

Mette Thomsen[1,2], Morten Dahl[1,2,3], Peter Lange[2,4,5,6], Jørgen Vestbo[7,8], and Børge G. Nordestgaard[1,2,4]+
Author Affiliations

- **OBJETIVO: 3 BIOMARCADORES RELACIONADOS CON COMORBILIDADES EN EPOC.**
- **METODO: 8,656 PACIENTES DANESES CON EPOC X 5 AÑOS, HASTA INGRESO HOSPITAL POR COMORBILIDAD MAYOR..**
- **MEDIDAS: PROTEINA C REACTIVA (>3) , FIBRINOGENO (>330 MG%), LEUCOCITOS SANGRE (>9000)**
- **RESULTADOS: CARDIOPATIA ISQUEMICA, IAM, ICC, DIABETES 2, CANCER PULMON, NEUMONIA, TEP, FRACTURA CADERA, DEPRESION.**
- **RIESGO RELATIVO:**
- **2,19 PARA CARDIOPATIA ISQUEMICA SI 3 MARCADORES ELEVADOS. 2,32 PARA IAM;**

  2,62 PARA ICC; 3,54 PARA DIABETES 2; 4 PARA CANCER;
  2,71 PARA NEUMONIA.

  NO RIESGO TEP, FX CADERA, DEPRESION.

AJRCCM 2012; 186: 982

Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense?
Vanessa M McDonald, Isabel Higgins, Lisa G Wood, Peter G Gibson
Thorax 2013;68:691–694

TRATAMIENTO EN BASE A 3 ACTUACIONES:

1) INFLAMMOMETRIA
2) MULTIDIMENSIONAL
3) IMPACTO INDIVIDUAL

Inflammation-based algorithm: Airway inflammation

- Eosinophilic (sputum eosinophil count %>3) — ICS 500 μg twice daily (beclomethasome equivalent) and prednisolone.
- Neutrophilic (sputum neutrophil count %>61) — Azithromycin 250 mg daily for 3 months
- Mucus hypersecretion — Positive EEP device (Acapella)
- — Hypertonic saline 6% twice daily, nebulised
- Systemic inflammation (CRP >3 mg/litre) — Simvastatin 20 mg daily for 3 months
- If systemic inflammation and neutrophilic airway inflammation were present doxycycline was used in place of azithromycin to avoid coadministration of simvastatin and azithromycin.

Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense?
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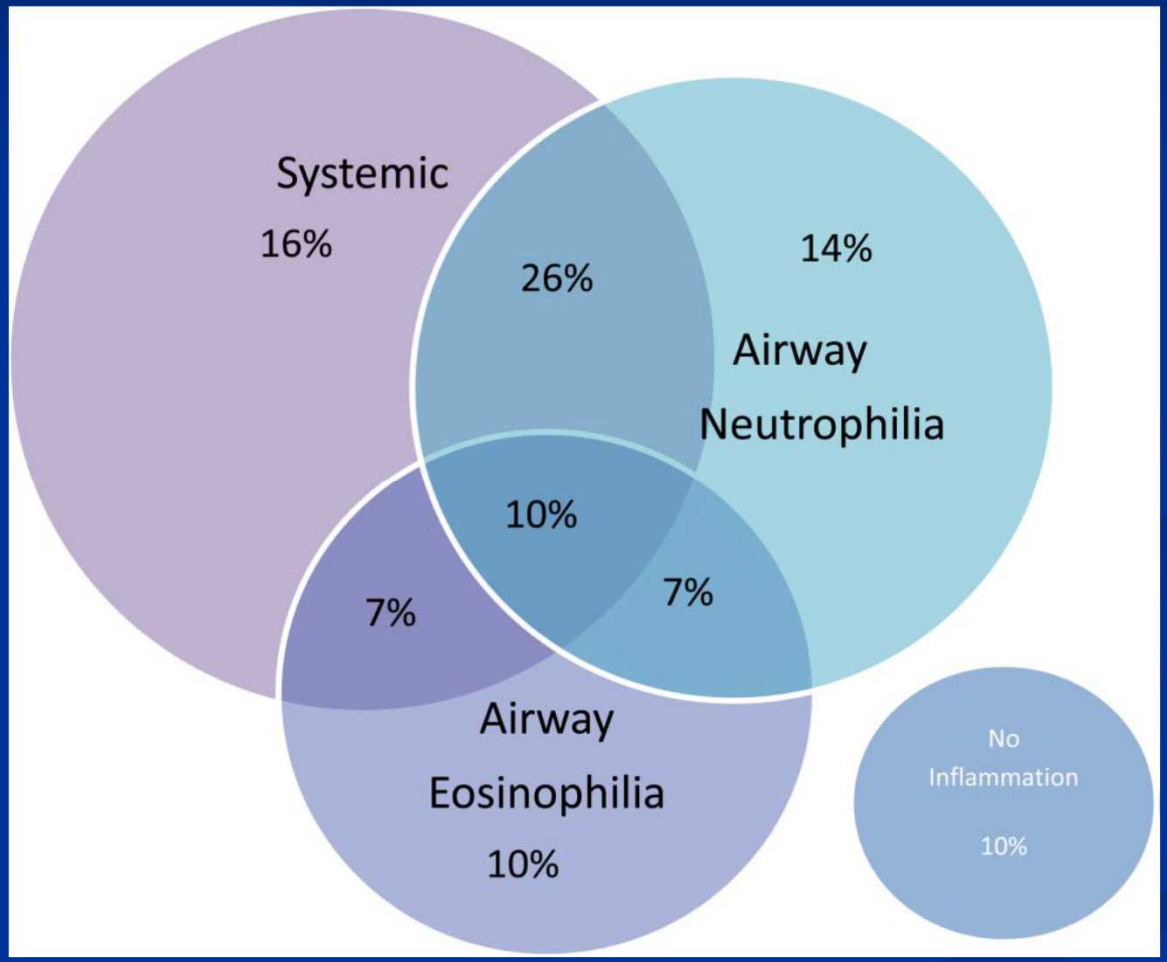

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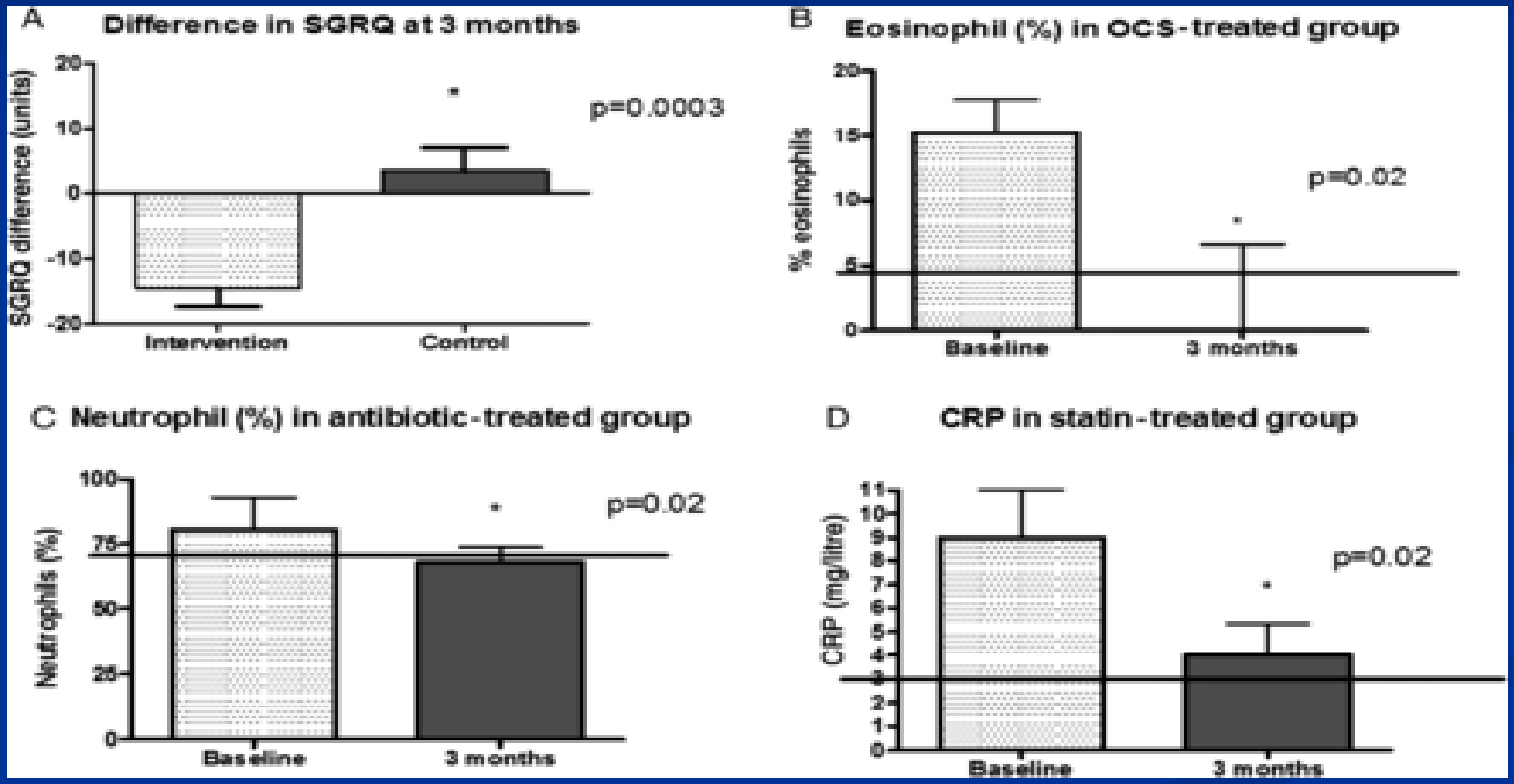

DIFERENTES BIOMARCADORES EXAMINADOS RECIENTEMENTE

- **Exhaled breath condensate biomarker** airway inflammation are shown to have considerable **variability**, due to technical issues concerning both sample collection and analysis. *ERJ August 1, 2008.*
- **Fibrinogen Aα-Val^{360}: a marker of neutrophil elastase** and COPD disease activity - EN ESPUTO.
- **Airway gene expression in COPD** is dynamic with inhaled corticosteroid treatment and reflects biological pathways associated with disease activity. *Thorax doi:10.1136/thoraxjnl-2012-202878. Postma et al*
- **Plasma desmosine concentrations** are elevated in patients with stable COPD but reduced lung diffusing capacity. **Urinary desmosine** concentrations are raised during exacerbations of COPD, after elastin degradation. *Thorax 2012;67:502.*
- **Three-year follow-up of Interleukin 6 and C-reactive protein** in chronic obstructive pulmonary disease. The systemic inflammatory process, evaluated by IL-6, seems to be persistent, progressive and associated with mortality and worse physical performance in COPD patients**, not the C-reactive protein**. *Respiratory Research 2013, 14:24*
- **Longevity in Male and Female Joggers**: The Copenhagen City Heart Study. 18000 hombres y mujeres seguidos 30 años. **Los que corren** hombres viven 6 años y las mujeres 5,6 años más. *Am. J. Epidemiol. (2013) 177 (7): 683.*
- **Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD**: a randomised controlled trial. **No significant changes in biomarkers of airway inflammation** (interleukin-8 and myeloperoxidase) and systemic inflammation (C-reactive protein) or airway and systemic oxidative stress (8-isoprostane). *ERJ 2012; 39:1377.*

Systemic biomarkers in the evaluation and management of COPD patients: are we getting closer to clinical application?

Kostikas K, Bakakos P, Papiris S, Stolz D, Celli BR

Table 1. Synoptic Presentation of Major Candidate Systemic Biomarkers in COPD in Association with Disease Activity

Biomarker	Clinical Implication
CRP	Increased in COPD [28, 29]; associations with PaO_2 and 6MWD [32]; increased risk for cardiovascular injury [33]
Fibrinogen	Association with FEV_1 [36]; increased levels associated with faster FEV_1 decline [35, 71]
TNF-α	Increased levels and association with cachexia in early studies [29, 37]; detectable only in a small portion of COPD patients in the ECLIPSE cohort [38, 39]; lower in COPD compared to smokers without COPD [38]; increased levels associated with accelerated loss of FFM in patients with cachexia [40]
SP-D	Increased in COPD - not associated with severity [42]
CC-16	Reduced in COPD - weak correlation with disease severity in ex-smokers [45]
Desmosines	Increased in COPD [48, 49]; correlated with FEV_1 and DLco [48]

CC-16: Clara cell secretory protein-16; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DLco: diffusing capacity of the lung for carbon monoxide; FFM: fat-free mass; FEV_1: forced expiratory volume in 1 sec; PaO2: partial pressure of oxygen; SP-D: surfactant protein-D; TNF-α: tumor necrosis factor-alpha; 6MWD: 6-minute walking distance.

Curr Drug Targets. 2013 Feb;14(2):177-91

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Table 2. Synoptic Presentation of Major Candidate Systemic Biomarkers in COPD as Predictors of Clinically Relevant Outcomes

Biomarker	Clinical Implication
CRP	Increased levels associated with increased risk for hospitalization [69]; data on mortality inconsistent [30, 69, 70]
Fibrinogen	Increased levels associated with increased risk for AECOPD and hospitalization [71, 72]; increased levels are associated with increased mortality risk [73]
Fibronectin/CRP ratio	Increased levels associated to cardiovascular mortality, more prominently in current smokers [76]
Adiponectin	Inversely related to hospitalizations and mortality from coronary heart disease and to cardiovascular disease but were positively related to deaths from respiratory causes [77]
PARC/CCL-18	Increased levels associated with increased risk for all-cause mortality and cardiovascular hospitalization and mortality [78]
Copeptin	Increased levels associated with long-term clinical failure after an AECOPD [80]
Pro-adrenomedullin	Increased levels associated with increased mortality [81]
BNP	Increased levels at the onset of an AECOPD associated with ICU admission but not with short- or long-term mortality [83]
MR-proANP	Increased levels associated with worse 2-year survival [84]
Troponin T	Increased levels on admission associated with increased short- and long-term mortality [85, 86] and increased levels at discharge associated with increased risk of hospitalization at 6 months [87]
NT-proBNP	Increased levels associated with 30-day mortality [86] and 6-month mortality [87]
IL-6	Improvement in the prediction of mortality in addition to clinical parameters [89]; a panel of 6 biomarkers (IL-6, neutrophil counts, fibrinogen, hs-CRP, CCL-18/PARC, and SP-D) further improved prediction of mortality [89]

BNP: B-type natriuretic peptide; CRP: C-reactive protein; AECOPD: acute exacerbations of COPD; CCL-18: chemokine ligand 18; IL: interleukin; MR-proANP: midregional proatrial natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; PARC: pulmonary and activation regulated chemokine; SP-D: surfactant protein-D.

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Table 3. Synoptic Presentation of Major Candidate Systemic Biomarkers in COPD of Potential Clinical Use in AECOPD

Biomarker	Clinical Implication
CRP	Increased in Anthonisen type I [80]; may improve the diagnosis of AECOPD when added to major symptoms [100]; identification of patients with late recovery and risk of recurrent AECOPD [111]
SAA	More sensitive than CRP in the identification of moderate/severe AECOPD [102]; may identify bacterial infections [108]
IP-10	May help in diagnosis of HRV infection [107]
CXCL10	Identification of viral infections [108]
Blood eosinophils	Identification of AECOPD with sputum eosinophilia [108]
Copeptin	Association with length of hospitalization and death during hospitalization [80]
Pro-adrenomedullin	Association with length of hospitalization [81]
Pro-endothelin-1	Association with length of hospitalization [81]
Albumin	Association with length of hospitalization [109]
Troponin-T	Association with length of hospitalization [110] and 30-day mortality [86]

AECOPD: acute exacerbations of COPD; CRP: C-reactive protein; CXCL10: chemokine (C-X-C motif) ligand 10; HRV: human rhinovirus; IP-10: interferon-gamma-inducible protein 10; SAA: serum amyloid A.

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Table 4. Synoptic Presentation of Major Candidate Systemic Biomarkers in COPD Associated with Treatment Response and Guidance

Biomarker	Clinical Implication
CRP	Responsive to oral CS and high-dose ICS in a small trial [115]; may be useful to guide antibiotic treatment [104]
SP-D	Significant reduction after 8 weeks treatment with ICS and ICS/LABA combination [117]; reductions associated with FEV_1 and quality of life improvements [117]; reduced by oral CS [42]
PARC/CCL-18	Reduced by oral CS [78]
Procalcitonin	Reduction in the use of antibiotics in patients with AECOPD without difference in outcomes [126]
Blood eosinophils	Reduction in the use of systemic CS [132]

AECOPD: acute exacerbations of COPD; CRP: C-reactive protein; CCL-18: chemokine ligand 18; CS: corticosteroids; ICS: inhaled corticosteroids; LABA: long-acting β2-agonists; PARC: pulmonary and activation regulated chemokine; SP-D: surfactant protein-D.

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CONCLUSIONES BIOMARCADORES EPOC 2014

- Reproducible en enfermedad estable: Fibrinogeno, SP-D and CC-16 fueron reproducible en enfermedad estable en 3 meses en ECLIPSE. La densidad del TAC, la SP-D y el Recetor soluble de la Glicación eran las predictoras de progresión.
- La mayoría son inespecíficos para EPOC y pulmón. Excepción para algunos que sí son específicos (SP-D, CC-16, and PARC/CCL-18) y prometen.
- La presencia de comorbilidades, la mayoría con enfermedad cardiovascular y sindrome metabólico son un elemento de confusión en la evaluación de biomarcadores sistémicos.
- Hay evidencia de que la inflamación pulmón/vías aéreas está disociada de inflamación sistémica, sugiriendo que expresan procesos separados. La mayoría de los biomarcadores anteriores no están relacionados con severidad.
- La mayoría de los Biomarcadores representan consecuencias más que mediadores de la patogénesis y actividad de la enfermedad.
- El uso de Biomarcadores llevará a menor uso de antibióticos y corticoides sistémicos.

CONCLUSIONES BIOMARCADORES EPOC 2014

- LAS **ESTATINAS REDUCEN LA IL-6 Y LA PCR** Y REDUCEN LA ENFERMEDAD SISTEMICA.
- LA **ACTIVIDAD FISICA Y EL CORRER** CONLLEVAN A REDUCCIÓN DE LOS BIOMARCADORES.
- EL **CONSUMO DE FRUTA, LA FIBRA EN DIETA, Y ANTIOXIDANTES** REDUCEN LOS BIOMARCADORES.
- LA **ACETYL CISTEINA, ROFLUMILAST,** REDUCE LA HIPERINSUFLACION DINÁMICA.
- **LA PROCALCITONINA Y PCR** DISTINGUEN NEUMONIA DE AEPOC
- LA **PROT. C REACTIVA > 48 MG/L** TIENE SENS. DEL 91% Y ESPECIF.93% PARA NEUMONIA